The second meal phenomenon in type 2 diabetes

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**Objective** - In health, the rise in glucose after lunch is less if breakfast has been taken. We evaluated the second-meal effect in Type 2 diabetes.

**Research Design and Methods** - Metabolic changes after lunch in 8 obese Type 2 diabetic subjects were compared on 3 days: breakfast taken; no breakfast; no breakfast but intravenous arginine 1 hour pre-lunch).

**Results** - Despite comparable insulin levels, the rise in plasma glucose after lunch was considerably less if breakfast had been taken (0.68±1.49 vs. 12.32±1.73 vs. 7.88±1.03 mmol.h/l; p<0.0001). Arginine administration almost halved the lunch rise in plasma glucose (12.32±1.73 vs. 7.88±1.03 mmol.h/l). The plasma FFA concentration at lunch time directly related to plasma glucose rise after lunch (r=0.67, p=0.0005).

**Conclusions** - The second-meal effect is preserved in Type 2 diabetes. Pre-meal administration of a non-glucose insulin secretagogue results in halving the postprandial glucose rise and has therapeutic potential.
The effect of a prior meal in decreasing the rise in blood glucose after a subsequent meal was first recognised almost a century ago (1). It has repeatedly been confirmed in healthy subjects but, tests with intravenous or oral glucose suggested that the second meal effect does not occur in type 2 diabetes (2-4). We observed incidentally that a second meal in subjects with type 2 diabetes brought about a 70% lesser rise in blood glucose (5).

This study was designed to determine whether the second meal phenomenon is present in type 2 diabetes, and if so, whether this can artificially be induced as a possible therapeutic approach.

RESEARCH DESIGN AND METHODS

Subjects: 8 subjects with type 2 diabetes were recruited (56.1 ± 2.8 years, BMI 36.0 ± 2.5 kg/m², HbA1c 6.7 ± 0.2 %, diabetes duration 8.1 ± 0.5 years, diet and/or metformin treatment). Ethics committee permission was obtained.

Study Methods: The metabolic response to a standard lunch was studied on 3 separate days in random order with 2-4 weeks between studies. On Day A the subjects had a standard breakfast followed by the standard lunch. On Day B breakfast was omitted. On Day C, breakfast was omitted and arginine was infused 1 hour before lunch. The details of metabolic testing, arginine administration and hormone and metabolites assays were as previously described (5; 6).

Meal composition: The standard breakfast consisted of 50 g muesli, 100 g milk, two slices of toast (56 g), 20 g marmalade, 20 g margarine and 200 ml orange juice (106 g carbohydrate, 18 g fat, 15 g protein, 646 kcal). The standard lunch comprised a cheese sandwich, orange juice 200 ml, yogurt 170 g and 150 g jelly (103 g carbohydrate, 30 g fat, 44 g protein, 858 kcal).

Statistical Analysis: Data are presented as mean ± SE. One way ANOVA and linear correlation were performed using MINITAB (State College, PA).

RESULTS

Glucose: The rise in plasma glucose after lunch was greatest on the day without breakfast and almost 40% lower on the arginine day (0.68±1.49 vs. 12.32±1.73 vs. 7.88±1.03 mmol.h/l; p<0.0001)(Figure 1a).

On Day A breakfast increased plasma glucose from 7.6±0.4 to 13.3±1.0 mmol/l at 2 hours and 8.4±0.7 mmol/l at 4h. On Day B (no breakfast), plasma glucose fell from 8.0±0.4 to 6.5±0.3 mmol/l by 4h. Two hours after the test lunch plasma glucose was 8.6±0.6 mmol/l on Day A compared with 10.9±0.8 mmol/l on Day B.

On Day C, fasting plasma glucose fell from 7.6±0.6 mmol/l to 6.6±0.6 mmol/l at 3 hours just prior to the arginine infusion and was 7.1±0.7 mmol/l at 4h.

Serum insulin and C-peptide:

Fasting serum insulin was similar on each of the days (127±23, 140±48 and 115±27 pmol/l for Days A, B and C respectively; p=0.87). The post lunch serum insulin concentrations were comparable on Days A, B and C (1918±45 vs. 2040±75 vs. 1472±40 pmol.h/l; p =0.76). On Day A, serum insulin peaked at 954±237 pmol/l 2 hours after breakfast. On Day C, insulin concentrations increased sharply after 30 minutes of the arginine infusion (418±177 pmol/l) but returned to the baseline (157±37 pmol/l) before lunch.

Insulin: C-peptide ratios were similar after the test lunch on all three experimental days (144±23, 185±47 and 168±31 pmol/nmol; p=0.73 at 2 hours after lunch).

Glucagon and catecholamines:

Fasting glucagon levels were similar on each of the 3 experimental days (87±11, 83±9 and 83±7 pg/ml). On Day C, the arginine infusion induced a 3-fold increase in glucagon
concentrations after 30 minutes to a short lived peak of 263 ± 28 pg/ml.

Pre-lunch and 30 minute post lunch adrenaline levels were similar on each day (0.32±0.06, 0.36±0.04, 0.37±0.04 nmol/l; p=0.77 and 0.34±0.04, 0.41±0.06, 0.39±0.04 nmol/l; p=0.67).

**Plasma FFA:** Fasting plasma FFA were similar on the 3 study days (0.64 ± 0.07, 0.65 ± 0.9 and 0.67 ± 0.7 mmol/l; p=0.96). After breakfast on Day A, plasma FFA levels were suppressed within 2 hour to 0.18±0.04 mmol/l. On Day B, plasma FFA were 0.65±0.4mmol/l before and 0.27 ± 0.04 mmol/l 2h after lunch. On Day C, plasma FFA were suppressed by the arginine infusion (0.35 ± 0.04 mmol/l) and the lunch (0.18 ± 0.03 mmol/l 2 h after lunch). The concentration of plasma FFA was strongly related to the AUC of plasma glucose concentration after lunch (r=0.67, p=0.0005)(Figure 1b).

**CONCLUSIONS**

In obese type 2 diabetic subjects the rise in plasma glucose was 95% less after lunch when the lunch had been preceded by breakfast, confirming the occurrence of the second meal effect in type 2 diabetes. The effect on plasma glucose was similar or slightly greater than that in healthy subjects (73% decrease in post-lunch hyperglycaemia) (7). Substrate oxidation rates were unchanged across experimental days (data not shown). The plasma FFA concentration before lunch correlated positively with the post-lunch rise in plasma glucose after lunch. The post-lunch insulin profiles were similar on all test days.

The concept that the second meal phenomenon did not occur in type 2 diabetes derived from study of repeated intravenous glucose (3) although this has a poor effect upon insulin secretion (8). In contrast, a mixed meal or injection of amino acids brings about an increase in plasma insulin levels even in type 2 diabetes (8; 9).

The second meal phenomenon is not mediated by an acute effect on insulin secretion and FFA suppression must be considered. Increased FFA induces insulin resistance in humans (10; 11). Conversely, suppression of plasma FFA by acipimox acutely improves insulin action in type 2 diabetes by increasing glucose storage as muscle glycogen and decreasing hepatic glucose production (9; 12; 13). An increase FFA leads to an inhibition of net hepatic glycogen breakdown and increases gluconeogenesis (14). We recently observed that in normal subjects the second meal phenomenon was associated with increased rates of storage of lunch-time carbohydrate in muscle glycogen (7).

The present data demonstrate that under everyday conditions postprandial glucose metabolism in type 2 diabetes is facilitated by suppression of plasma FFA concentrations following a previous meal.

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REFERENCES

Second meal phenomenon and diabetes

A

B

AUC Glucose (mmol.h/l)

* Breakfast Lunch only Arginine

FFA (mmol/l)

AUC glucose (mmol.h/l)